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Race/ethnicity and challenges for optimal insulin therapy

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ABSTRACT

Aims: We aimed to review insulin dosing recommendations, insulin regulation and its determinants, glycaemic response to carbohydrates, and the efficacy and safety of insulin therapy in different races/ethnicities.

Methods: We searched for articles in PubMed and Google Scholar databases up to 31 March 2021, with the following keywords: "ethnicity", "diabetes", "insulin", "history of insulin", "insulin therapy", "food/rice", "carbohydrate intake", "insulin resistance", "BMI", "insulin dosing", "insulin sensitivity", "insulin response", "glycaemic index", "glycaemic response", "efficacy and safety", with interposition of the Boolean operator "AND". In addition, we reviewed the reference lists of the articles found.

Results: The differential effect of race/ethnicity has not yet been considered in current insulin therapy guidelines. Nevertheless, body size and composition, body mass index, fat distribution, diet, storage, and energy expenditure vary significantly across populations. Further, insulin sensitivity, insulin response, and glycaemic response to carbohydrates

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differ by ethnicity. These disparities may lead to different insulin requirements, adversely impacting the efficacy and safety of insulin therapy among ethnic groups.

Conclusions: Race/ethnicity affects glucose metabolism and insulin regulation. Until now, international guidelines addressing racial/ethnic-specific clinical recommendations are limited. Comprehensive updated insulin therapy guidelines by ethnicity are urgently needed.

1. Introduction

Diabetes is a major public health challenge of the 21st century. Currently, around 463 million people (20–79 years) live with diabetes, which corresponds to 9.3% of the global population. By 2045, this number is expected to rise to 700 million. Formerly considered "a disease of the wealthy", approximately 80% of those with diabetes now live in low- and middle-income countries [1]. Although diabetes is common across the world, ethnic disparities have been consistently reported in relation to diabetes prevalence and incidence, pathophysiology, mortality, and acute and long-term complications [1–3].

Several studies on racial differences in diabetes have shown higher prevalence and incidence rates among non-white populations [2,4,5]. Although the exact reasons remain unknown, these disparities likely emanate from multiple factors, including genetic, epigenetic, different pathophysiological patterns, lifestyle, and environment [2]. Worldwide, Hispanic, and Asian populations present a higher prevalence of diabetes than Europeans and Africans both in their native settings and among their diaspora [1,6]. Evidence suggests that the genetic background of Africans and East Asians makes them more and differentially susceptible to diabetes than Caucasians [7]. Diabetes prevalence also differs considerably among Hispanic and non-Hispanic Asian subgroups in the United States [4,6]. In a nationally representative survey of US adults from 2011 to 2016, the prevalence of diabetes was 12.1% for non-Hispanic white (NHW), whereas it was significantly higher for non-Hispanic black (NHB) (20.4%), Hispanic (22.1%), and non-Hispanic Asian adults (19.1%) [2].

The literature shows that non-Caucasians have higher mortality rates and risk of diabetes complications, after adjusting for confounders [8]. Approximately 4.2 million people died of diabetes in 2019, with marked heterogeneity across the globe. According to the International Diabetes Federation (IDF), death rates attributable to diabetes varied from 6.8% in sub-Saharan Africa, to 8.5% in Europe, around 11% in the Western Pacific region, almost 13% in South and Central America, approximately 14% in the North America, Caribbean, and South East Asia regions, and 16.2% in Middle East and North Africa [1]. In the US, NHB are 2.3 times more likely to die from diabetes than NHW, whereas the figures for Native Americans and Hispanics are 1.9 and 1.5x. Furthermore, Native Hawaiians and Filipinos living in Hawaii are 5.7 and 3.0 times more likely to die from diabetes than NHW [9]. Even in modern societies where diabetes care is available and accessible for great portion of the population, both micro- and macrovascular complications related to diabetes differ significantly among ethnic groups. Although a lower risk of cardiovascular disease (CVD) has been reported for ethnic minorities in the US, several studies suggest that Native Americans, Hispanics and NHB have an increased risk for lower extremity amputations than NHW [10]. Furthermore, Asians in the UK and the Netherlands, as well as Hispanics and blacks in the US have shown a higher risk of nephropathy and end-stage renal disease. Ethnic minorities in the US also seem to present an increased risk of retinopathy, whereas Algerians in France have a higher risk of neuropathy [8].

Differences in responsiveness to medicinal products have been commonly observed across ethnic groups. Although insulin has been applied in the treatment of diabetes for 100 years, scarce evidence exists regarding potential ethnic differences in response to insulin dosing and formulations. It has been reported that West African descendants (including African Americans and native Ghanaians) have higher degrees of insulin resistance than Caucasians [11,12]. Similarly, despite a higher average energy and fat intake, NHW have also shown lower insulin resistance than Hispanics [13]. Those ethnic differences in insulin sensitivity may affect recommendations on treatment type and dosage. Even though in insulin therapy the dose is individually titrated according to patients' needs and lifestyle, the recommended starting dose may vary across ethnic groups. Therefore, we aimed to review insulin dosing recommendations, insulin regulation and its determinants, glycaemic response to carbohydrates, and efficacy and safety of insulin therapy in different races/ethnicities.

2. Methods

A literature review was carried out to search for articles in PubMed and Google Scholar databases up to 31 March 2021. The following keywords were used: "ethnicity", "diabetes", "insulin", "history of insulin", "insulin therapy", "food/rice", "carbohydrate intake", "insulin resistance", "BMI", "insulin dosing", "insulin sensitivity", "insulin response", "glycaemic index", "glycaemic response", "efficacy and safety", with interposition of the Boolean operator "AND". Further, we retrieved the full text of relevant studies in the reference lists of the searched articles. Only articles in English were considered.

2.1. *Brief history of insulin*

In 1889, two German researchers, Oskar Minkowski and Joseph von Mering, found that when the pancreas gland was removed from dogs, the animals developed symptoms of diabetes and died soon afterward. This led to the idea that the pancreas was the site where "pancreatic substances" (insulin) were produced. In 1921, inspired by Mering' and Minkowki's studies, Paulescu performed a pancreatectomy in a dog, emulsified the pancreatic tissue and injected it into the jugular vein of the animal. He demonstrated that this pancreatic extract had an anti-diabetic effect [14].

In 1922, for the first time in the history of medicine, an insulin extract was administered to a 14-year-old boy in Toronto General Hospital. Nevertheless, this clinical experimentation was a failure. Following further refinements, a second series of injections effectively controlled glycaemia, glycosuria, and ketonuria. This marked the first successful administration of insulin to a type 1 diabetes patient and, ultimately, led to the development of commercially available insulin [15].

Important progress has been made over the last hundred years. The structure of insulin was delineated in 1955. In 1967, proinsulin was discovered and the radioimmunoassay for C-peptide was developed. In 1972, the U100 insulin was introduced to promote better accuracy in administration, and, in 1982, recombinant human insulin became available. In the 1990s, insulin pen delivery devices became available, followed by the discovery of short (1996) and long (2001) acting insulin analogues [14].

2.2. *Insulin dosing: Formulae and challenges in different ethnic groups*

Given the progressive nature of type 2 diabetes mellitus (T2DM), many patients eventually require and benefit from insulin therapy. According to the American Diabetes Association (ADA) [16], insulin for T2DM may be started to augment therapy with oral agents. Currently, basal insulin alone is a usual regimen applied in clinical practice. Starting doses can be estimated based on body weight (0.1–0.2 units/kg/day) and the degree of hyperglycaemia. Alternatively, ten units of basal insulin once daily can be added, with individualized titration over days to weeks as needed. Some individuals may also require doses of insulin before meals to reach glycaemic targets. Usually, a dose of 4 units or 10% of the amount of basal insulin at the largest meal or the meal with the highest postprandial excursion is applied for initiating therapy. In metabolically stable type 1 diabetes patients or those with T2DM who require replacement therapy, total daily insulin requirements are also estimated by the weight, with doses ranging from 0.4 to 1.0 units/kg/day (0.5 units/kg/day is a typical starting dose, with 50% of the daily dose as basal insulin and 50% as prandial). The longer-acting basal dose regulates overnight, fasting glucose, whereas shorter acting formulations control postprandial glucose levels. Current recommendations for prandial insulin dose are individualized based on carbohydrate intake, premeal glucose levels, and anticipated activity [16]. Nevertheless, specific features of insulin resistance, insulin secretion, and glycaemic response to carbohydrates in different populations have not yet been addressed in the formulae.

Historically, dosing guidelines have been based on clinical experience and retrospective studies of patients. The first formula proposed in 1922 was also weight based and calculated conservatively to prevent hypoglycaemia and preserve the limited amount of insulin available (Dose (ml) = body weight × insulin sensitivity of dogs / 2) [17]. In 1982, based upon clinical experience with human regular insulin, Skyler et al. [18] suggested that the total basal dose (TBD) should be about 40% of the total daily dose (TDD). In 1998, the "rule of 3" was proposed for estimating carbohydrate-to-insulin ratio (CIR = [3 × weight in lb]/TDD) [19]. Current formulae for estimating the correction factor (CF) are based on the suggestion by Davidson et al. [19] of the "1500 rule", later modified to "1700" (CF = 1700/TDD). These three formulae together became the foundation of the Accurate Insulin Management system. Subsequently, Walsh et al. [20], using retrospective pump download information, suggested that the CIR should be calculated from 450/TDD. Since the previous formulae had been based on regular insulin used in pump treatment, Walsh et al. proposed a modification to CF = 2000/TDD. Walsh essentially agreed with Davidson that the formula for estimating the CIR should be CIR=(2.6 × weight in lb)/TDD, reflecting the widespread use of rapid-acting insulin analogs (see Table 1 for a detailed description of the parameters used in the formulae) [20].

Currently, a consensus statement from the American Association of Clinical Endocrinologists/American College of Endocrinology [22], recommends the following formulae: TBD (U) = 50% of TDD, CIR = 450/TDD, and CF = 1700/TDD. Nevertheless, independent studies in Japan and the US using more rigorous designs suggested that traditional formulae overestimated basal insulin requirements and underestimated bolus requirements [23]. Results from the US showed that the TBD should be 40% of the TDD, whereas data from Japan reported a more appropriate TBD of 30% of the TDD. The Japanese diet with higher-carbohydrate and lower-fat proportions than the US diet possibly explains this difference. Further, Japanese studies also found that the CIR exhibited diurnal variability ranging from 300/TDD at breakfast to 400/TDD for lunch or dinner [23]. Hypothetical calculation has shown that the currently used formulae for estimating the CIR and CF may lead to underdosing of bolus insulin by as much as 12.8–50% [21].

High-fat, low-carbohydrate intake reduces the ability of basal insulin to suppress hepatic glucose production [24]. Since the American diet has higher-carbohydrate and lower-fat proportions, it could be assumed that the US recommendations for basal dose would be higher than in countries with lower-fat content in their diet. For the Asian Indian diet [25] (consisting of 78% carbohydrates and 13% fat), for instance, the total bolus dose should be much higher than the US diet, but the total basal dose would be less. Therefore, it is possible that the recommended TBD to be 50% of the TDD may be excessive for India, China, and other countries of similar diet composition [21]. The TBD/TDD ratio of < 30% in the Japanese studies supports this contention [23].

Table 1 – Definition of parameters used in insulin dosing formulae [21].

Parameters	Definitions
TDD	The total basal and prandial insulin dosage.
TBD	The fraction of TDD given as basal insulin.
CIR	A number that, when divided into the number of grams of ingested carbohydrates, indicates the units of insulin needed to lower blood glucose to a pre-meal value within 2–4 h.
CF	A number that, when divided into the difference between actual and target blood glucose, yields the number of extra units of insulin needed to lower blood glucose to the target range, within 2–4 h.

CF: correction factor, CIR: carbohydrate-to-insulin ratio, TBD: total basal dose, TDD: total daily dose

*Patients with greater insulin sensitivity will have higher CFs and CIRs

The discrepancies between traditional formulae and data from newer studies may be due to the more rigorous design of the latter. International differences in diet composition may also be important to consider when developing insulin dosing recommendations.

2.3. *Evolutionary roots of race/ethnic disparities in glucose metabolism and insulin regulation*

It has been hypothesized that depending on a population's genetic or evolutionary history, ethnic differences exist in the optimal states of glucose metabolism and insulin regulation. Human blood glucose levels have likely evolved toward their current equilibrium over thousands of years. As a response to genetic or environmental perturbations, the stability of blood glucose regulation has developed through a hyperbolic function of two variables: insulin sensitivity and insulin response [26,27]. Global migration in ancient days placed people in new environments, under different climate conditions, food availability and exposure to pathogens. These changes may have made some adjustments in factors that influence insulin sensitivity and secretion, such as body size and composition, energy expenditure, storage, and heat production. As these factors altered, novel genetic variations or mutations may have pushed some subpopulations to different points of stability [7,27].

Studies have found ethnic differences in the stabilization points of insulin sensitivity and insulin response to maintain the normal blood glucose levels. It has been observed that Africans have significantly lower insulin sensitivity and higher insulin response to glucose than Caucasians and East Asians. In contrast, East Asians present higher insulin sensitivity and lower insulin response than the other two groups [7]. In a meta-analysis of 74 study cohorts, Kodama et al. [7] calculated the hyperbolic relationship between insulin sensitivity and insulin response in three different populations. They used the mean values of the insulin sensitivity index (SI) and acute insulin response to glucose (AIRg) in normal glucose tolerance (NGT) cohorts and stratified distributions by ethnicity. As shown in Fig. 1, Caucasians clustered around the middle of the hyperbola, whereas African and East Asian subpopulations were in unstable extreme points in the curve. In these areas, small changes in one variable are associated with large nonlinear changes in the other variable. Therefore, it may be hypothesized that, in Africans, even a slight increase in insulin resistance in current days could lead to a rapid increase in the amount of insulin secretion necessary to maintain NGT [7]. Interestingly, it has been reported that African Americans have a twofold increased risk of developing T2DM compared with Caucasians [28]. On the other hand, given the observed limited capacity of insulin secretion in East Asians [29], it can also be speculated that even a small decrease in insulin secretion may lead to a rapid decrease in the threshold level of insulin resistance above which T2DM arises. This may possibly contribute to the high prevalence of diabetes in East Asia nowadays [7].

In any population, genetic predisposition, and environmental triggers likely account for the development of T2DM. The "thrifty genotype" hypothesis proposes that individuals with certain genetically driven metabolic features might have been selected for survival. In primeval times, when food availability was insecure, those who were metabolically "thrifty" had better odds of survival. When food was available, metabolic thriftiness ensured efficient storage of energy for use during famine. Nevertheless, with urbanization and immigration, now this genotype predisposes individuals to insulin resistance and diabetes [3,30]. In the early 1990s, Hales and Barker et al. [31] formulated an alternative explanation for the origins of T2DM, metabolic syndrome and CVD. The "thrifty phenotype" hypothesis suggests that poor intrauterine and infant nutrition produce permanent changes in glucose-insulin metabolism, preparing the individual for a life of starvation. Foetal malnutrition would result in insulin resistance and poor development of pancreatic β-cell mass and function. A limited insulin secretion capacity would not be detrimental to those who remained poorly nourished and thin, and, therefore, insulin sensitive. Nevertheless, if followed by overnutrition in childhood and adult life, an adverse foetal environment might lead to diabetes and other chronic diseases [31].

Historical data suggest that South Asians have become increasingly undernourished since the Mesolithic period. These long-term intergenerational influences, especially those adversely affecting maternal and/or early childhood, may have increased their risk to diabetes [32]. Bavdekar et al. [33] reported a significant association between low birth weight and high insulin resistance in 8-year-old Indian children. Other important contributing factors to diabetes susceptibility in this group include urbanization, decreased

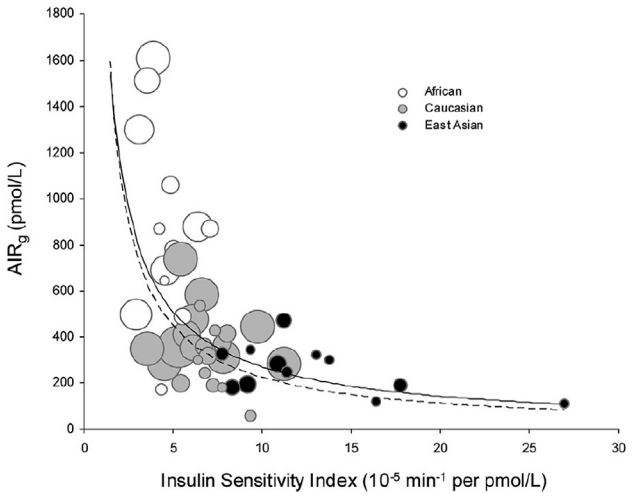

Fig. 1 – Ethnic differences in the relationship between insulin sensitivity and insulin response in normal glucose tolerance (NGT) cohorts. Scatter plot of insulin sensitivity index (SI) vs. acute insulin response to glucose (AIRg) measured in healthy African, Caucasian, and East Asian cohorts. Each circle corresponds to one study cohort. Each circle area is proportional to the cohort sample size. The solid line is the curve calculated in the meta-analysis of Kodama et al. [7] [ln(AIRg) = −0.915 × ln(SI) − 2.82]. The dashed line is the curve of Kahn et al. [26] describing healthy Caucasians [ln(AIRg) = −1.0 × ln(SI) − 3.80]. Figure by Kodama et al. Non-commercial creative commons license.

physical activity, higher intake of fat and processed food, increased mental stress, and migration to more affluent countries [34].

In recent history, several nations have suffered from famine. At the end of World War II (1944–1945), severe famine affected the western region of the Netherlands. The Dutch Hunger Winter Famine lasted 5 months, hit people of all social classes and was followed by growing prosperity in the post-war period. Moreover, it impacted foetal nutrition and early development, with resulting epigenetic changes that were linked to an increased risk of T2DM decades later [35]. Prenatal exposure to famine was related to impaired glucose tolerance (IGT) in adulthood and this seemed to be mediated by an insulin secretion defect [35,36].

Similar rises in the prevalence of T2DM have also been observed years after famine in Ukraine [37], Cambodia [38] and China [39]. Individuals exposed to the 1932–1933 Ukraine Famine during early gestation were 1.5-fold more likely to develop T2DM as adults than Ukrainians not affected by the famine [37]. After decades of severe food shortages in 1975–1979, T2DM prevalence in Cambodia rose to levels seen in developed nations [38]. Foetal exposure to the Chinese famine (1959–1961) exacerbated the association between obesity and adult risk of incident T2DM, as well as the association between hypertension and CVD [39].

2.4. *Glycaemic response to carbohydrates in different ethnic groups*

The glycaemic index (GI) represents the ability of a carbohydrate food to raise blood glucose levels [40]. It has been assumed that the glycaemic potential of certain food is independent of metabolic or demographic differences of the consumer. Nevertheless, different glycaemic responses to the same carbohydrate-containing food or glucose load have been reported across populations [41]. Venn et al. [41] observed that Asians present higher glycaemic responses than Caucasians following a common breakfast cereal (63% higher) and a beverage containing 50 g of glucose (29% higher). For an identical carbohydrate load, South Asians exhibit postprandial glucose peaks that are 2–3 times larger than Caucasians [40]. Furthermore, it has been reported that Hispanics have lower glycaemic excursions after evening meals than Caucasians, whereas Asians show greater excursions after breakfast than Caucasians [42]. Thai, Vietnamese, and Chinese lean young adults showed significantly higher postprandial glycaemia than European Caucasians after a bread meal (75 g carbohydrate) [43].

Traditional Asian diets are known to improve postprandial glucose profile at similar calories and even at greater carbohydrate content than Western diets [44]. Further, low GI Asian meals were shown to improve glycaemic response and even to increase fat oxidation [45]. Until the early 1970s, most traditional Asian diets were less milled or polished. Undermilled rice is nutritionally superior (richer in fibre, polyphenols, and vitamin E) than the fully milled white rice. However, during the last decades, hand-pounded rice has been increasingly replaced with white rice in many Asian countries. A recent study of 132,373 participants has shown that higher consumption of white rice is associated with an increased risk of incident diabetes in South Asia [46]. Ethnic differences have been observed in glycaemic responses to several varieties of rice. Kataoka et al. [47] reported that Chinese people had 60% greater glycaemic responses for five rice varieties than Europeans. Additionally, the GI for four rice varieties was approximately 20% greater in the Chinese [47].

Ethnicity is therefore an important factor in the contribution of postprandial glucose to glycated haemoglobin (HbA1c) levels. Given the higher intake of carbohydrates and greater glycaemic responses to the same glycaemic load in Asians, it is likely that they may have different insulin requirements especially higher mealtime insulin doses. Overall, more well-designed studies should be conducted in different populations to elucidate how dietary carbohydrates could be targeted to optimize blood glucose regulation. Including low GI foods may benefit Asians who habitually consume higher refined carbohydrate cereal staple diets than Europeans.

2.5. *Race/ethnic differences in determinants of insulin resistance and secretion*

Ethnic differences have been consistently observed on the mean values of height, weight, body mass index (BMI), body composition, and fat distribution. In general, Africans have less visceral fat area but more skeletal muscle and bone mineral mass than Caucasians, even though they tend to have similar body sizes [7]. On the other hand, East Asians have smaller mean height, weight, BMI and less mean total visceral fat volume than Africans and Caucasians [48]. South Asians often present higher body fat and lower lean muscle mass at the same or lower BMIs compared with white people (the “high body fat-normal weight/BMI-low muscle mass” phenotype) [49].

Although Africans have less intra-abdominal visceral fat than Caucasians, it has been observed that they are more insulin resistant, have greater insulin secretion and lesser insulin clearance than white people [50]. In this scenario, the expected positive association between visceral fat and insulin resistance is not applied. Nevertheless, it is possible that the African’s large amount of muscle and bone mass affects insulin sensitivity determinants, potentially leading to insulin resistance and increased insulin response. A higher baseline insulin secretion or lower insulin clearance may be also necessary to keep and grow the great amount of muscle and bone in this population [7]. Additionally, it has been observed that Africans have lower ectopic and greater peripheral (gluteofemoral) fat deposition than their European counterparts. This may indicate that either Africans are more sensitive to the effects of ectopic fat deposition or that ectopic fat is not an important mediator of T2DM in this population [50].

As addressed previously, healthy East Asians have a lower AIRg compared with Africans and Caucasians. It is likely that this may be a consequence of either 1) high insulin sensitivity due to low visceral fat content in healthy individuals or 2) lower baseline insulin secretion or higher insulin clearance sufficient to maintain a smaller body size compared with the other two groups. Furthermore, in the transition from NGT to IGT, insulin sensitivity may be markedly reduced,

while insulin response does not change significantly in East Asians. Nevertheless, insulin response may be rapidly reduced from IGT to T2DM [7].

It has been suggested that the pathogenesis of T2DM may differ in Asian populations compared with Caucasians. T2DM develops in Asian patients at a younger age and lower levels of BMI and waist circumference than white populations [51,52]. In fact, the BMI cutoff points for normal weight, overweight, and obesity were revised for Asians, and are now lower than the international classification criteria [53]. South Asians are disproportionally predisposed to diabetes. The underlying risk factors include higher insulin resistance, impaired β-cell function, an abnormal adipokine profile, and certain high risk genetic polymorphisms [34]. In the 1980s, Mohan et al. [54] observed that basal insulin levels and insulin response to a glucose load were higher in Asian Indians than Europeans. These results indicated that Asian Indians need higher levels of insulin to maintain euglycaemia and secrete higher amounts of insulin in response to the same glucose load [54]. Scholfield et al. [55] reported that Asian Indian vegetarians had significantly higher insulin levels than American vegetarians both in the fasting state and after an oral glucose load. Although they presented comparable diets, Asian Indians were more likely to be insulin resistant [55].

Given the same BMI, South Asians have higher total body fat and abdominal adipose tissue (both subcutaneous and visceral fat) than Caucasians [49]. This tendency to abdominal adiposity can result in increased fatty acid influx to the liver, impaired adipokine production, fatty liver, and hepatic insulin resistance [49,56]. Ectopic hepatic and intramyocellular fat deposition are important determinants of insulin resistance, which may propagate a vicious cycle with higher ectopic fat deposition in the liver and islets, hepatic insulin resistance, β-cell dysfunction and T2DM [49,57]. It has been suggested that this predisposition to adiposity and insulin resistance begins during foetal development. Yajnik et al. [58] found that Indian babies were lighter and smaller than babies born in the U.K., but preserved body fat (the thin–fat Indian baby). This body composition might persist later in life, resulting in an insulin-resistant state [58].

Asians have shown a decreased insulin secretion capacity which further increases the risk of diabetes [7,32]. The underlying mechanisms are yet to be determined; however, it may be explained by lower β-cell mass, impaired β-cell function and/or genetic influences [32]. In the US, it was observed that non-diabetic adult South Asians and Chinese had the lowest insulin secretion, compared with Hispanics, African Americans, and whites [4]. In the pathogenesis of T2DM, it is usually described that high insulin resistance may trigger increased insulin production to maintain normoglycaemia, which can result in β-cell failure over the time. Nevertheless, in Asian Indians, β-cell dysfunction appears to be the primary aetiological factor in the development of T2DM [59]. Therefore, targeted interventions to preserve or improve beta cell function and specific pharmacological approaches may be necessary in this population.

2.6. *Efficacy and safety of insulin therapy by race/ethnicity*

Race/ethnicity poses a challenge for optimal treatment in T2DM patients. So far, most clinical trials have been conducted primarily among white individuals. The lack of racially/ethnically diverse participants in diabetes clinical trials raises concern for the efficacy and safety of a given insulin regimen in different populations [42].

In a post hoc analysis of pooled data from 11 multinational clinical trials involving 1455 patients with T2DM, the metabolic response to insulin therapy differed significantly across

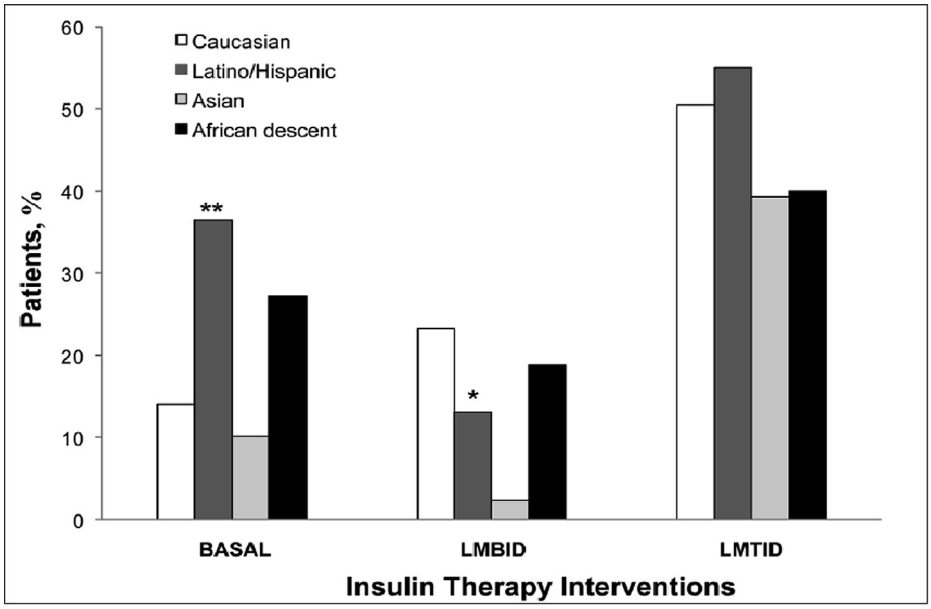

Fig. 2 – Racial differences in achieving HbA1c level < 7% with ≥ 12 weeks of insulin therapy. Single asterisk indicates p < .05 and double asterisk p < .01 vs Caucasians. BASAL = insulin glargine or neutral protamine Hagedorn; LMBID = insulin lispro mix 75/25 twice daily; LMTID = insulin lispro mix 50/50 three times daily. Figure by Davidson et al. [42]. Non-commercial creative commons license.

ethnicities, depending on the insulin type and regimen intensity. Hispanics showed better glycaemic control than Caucasians with a 12- to 24-week regimen of basal therapy. Nevertheless, after 12 to 16 weeks of insulin lispro mix 75/25 twice daily, Hispanic, and Asian patients had poorer overall glycaemic control than Caucasians (Fig. 2). Furthermore, Asians experienced higher incidence and rate of severe hypoglycaemia than Caucasians with intensified premixed insulin therapy (insulin lispro mix 50/50 three times daily) [42]. In a retrospective case analysis of 280 T2DM patients treated for 12 months with insulin (regimen not specified), significantly greater HbA1c reductions were observed in African/Caribbean patients than in Caucasians or Asians, despite significantly smaller weight-adjusted insulin doses [60].

It has been reported that glycaemic control varies significantly by race/ethnicity. Despite controlling for factors affecting glycaemia, HbA1c levels are often significantly higher in non-Caucasians with T2DM, IGT or NGT. In a clinical trial involving 2094 patients from 11 countries, HbA1c was significantly higher in Hispanics, Asians, Africans, and patients of other racial/ethnic groups than Caucasians [61]. In a meta-analysis by Kirk et al. [62], African Americans and Hispanics had higher HbA1c values than NHW, independently of study design, data collection methodology, and type of medical care. The higher therapeutic failures in non-white populations [63] may suggest that ethnic-based insulin dosing and formulations are needed.

3. Conclusions

Until now, racial/ethnic-specific clinical practice recommendations are limited in international guidelines. Few studies have addressed outcome differences in glycaemic control related to race/ethnicity and specific insulin regimens.

It has been shown that treatment response to insulin therapy varies by race/ethnicity and warrants future large trials. Future prospective clinical trials should include subjects in their natural habitat (for instance, Africans in Africa, South Asians in South Asia, Chinese in China) and where they migrated to, as well as Europeans, South and Central Americans, etc. This kind of study should be conducted under International respected bodies, like IDF or in collaboration with the World Health Organization (WHO). The trials should be targeted to the efficacy and safety of different insulin regimens in diverse populations, considering their body and fat composition and specific food habits.

Given the high and increasing prevalence of T2DM particularly in non-white populations, more studies are needed to better understand the impact of race/ethnicity on the differential responses to insulin therapy. This may provide more personalized and targeted management strategies.

Definition of race/ethnic groups

South Asian: refers to Asian Indian, Pakistani, Sri Lankan, Bangladeshi, Nepali, Bhutanese, Afghan, and Maldivian. East Asian: refers to Japanese, Chinese, and Korean. Southeast Asian: refers to Filipino, Vietnamese, Cambodian, Laotian, Thai, Indonesian, Malaysian, Singaporean, and Hmong. Hispanic: refers to Puerto Rican, Cuban or Cuban American, Dominican (Republic), Mexican or Mexican American, Central or South American. Non-Hispanic Black (NHB): individuals of African descent or who self-identify as black or African American. Non-Hispanic Asian: non-Hispanic persons who do not self-identify as black and have origins in any of the Asian countries. Non-Hispanic White (NHW): non-Hispanic individuals not falling into the other categories who self-identify as white. Native American: refers to American Indians and Alaska Natives.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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